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REVIEW

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Noninvasive assessment of hepatic decompensation

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Abstract

Noninvasive tests (NITs) are used in all aspects of liver disease management. Their most prominent break-through since the millennium has been in advancing early detection of liver fibrosis, but their use is not limited to this. In contrast to the symptom-driven assessment of decompensation in patients with cirrhosis, NITs provide not only opportunities for earlier diagnoses but also accurate prognostication, targeted treatment decisions, and a means of monitoring disease. NITs can inform disease management and decision-making based on validated cutoffs and standardized interpretations as a valuable supplement to clinical acumen. The Baveno VI and VII consensus meetings resulted in tangible improvements to pathways of care for patients with compensated and decompensated advanced chronic liver disease, including the combination of platelet count and transient elastography to diagnose clinically significant portal hypertension. Furthermore, circulating NITs will play increasingly important roles in assessing the response to interventions against ascites, variceal bleeding, HE, acute kidney injury, and infections. However, due to NITs' wide availability, there is a risk of inaccurate use, leading to a waste of resources and flawed decisions. In this review, we describe the uses and pitfalls of NITs for hepatic decompensation, from risk stratification in primary care to treatment decisions in outpatient clinics, as well as for the in-hospital management of patients with acute-on-chronic liver failure. We summarize which NITs to use when, for what indications, and how to maximize the potential of NITs for improved patient management.

Abbreviations: 2D, 2-dimensional; ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; ALD, alcohol-associated liver disease; cACLD, compensated advanced chronic liver disease; CSPH, clinically significant portal hypertension; ELF, Enhanced Liver Fibrosis; FIB-4, Fibrosis 4 Index; HRS, hepatorenal syndrome; LSM, liver stiffness measurement; MASLD, metabolic dysfunction–associated steatotic liver disease; MRE, magnetic resonance elastography; NFS, nonalcoholic fatty liver disease fibrosis score; NGAL, neutrophil gelatinase–associated lipocalin; NITs, noninvasive tests; NSBB, nonselective beta-blockers; pSWE, point shear-wave elastography; SSM, spleen stiffness measurements; TE, transient elastography.

INTRODUCTION

The evolvement and documentation of the benefit of noninvasive tests (NITs) in clinical hepatology has accelerated in recent years.[1] While the assessment of patients from their signs and symptoms remains essential in daily clinical practice, objective measures are important to standardize patient management. The Food and Drug Administration (FDA) defines a noninvasive test as a medical test that does not cut the skin or enter the body. However, blood sampling from simple venipuncture and surplus samples of, for example, body fluids from samples taken for noninvestigational purposes are also considered noninvasive.[2] Many NITs were developed to diagnose and assess severity at the early stages of disease. However, NITs may be equally valuable when applied at more advanced stages of disease, to patients with decompensated disease, or to patients at risk of decompensation. Recent developments have provided a wealth of data to support the applicability of NITs in these patient groups.[3] In addition to serving a diagnostic purpose and guiding decisions on treatment, several NITs also provide important prognostic information.[3–5] While diagnostic NITs for patients with suspected liver disease are often used sequentially along a health care pathway, secondary and tertiary care more often use NITs in parallel, looking for concordant results to support management decisions.[6] This review provides an overview of NITs that are used to inform clinical decision-making in patients with decompensated disease or patients at risk of decompensation.

Noninvasive tests to guide clinical decision-making

Conceptually, NITs are only relevant when there is a decision to be made and when the test result can influence the decision.[7] If the physician is certain about the next steps in the management of his/her patient, or the NIT provides no information to support or contradict the decision, then noninvasive testing is superfluous. For patients at risk of decompensation, NITs often inform decisions regarding whether to start, adjust, or stop interventions to halt the development of first decompensation, avoid further decompensation, improve quality of life, reduce the risk of hospitalization, or decrease the risk of mortality (Table 1).[8]

To better understand how NITs support and qualify clinical decisions, it is useful to understand Bayes' theorem (Figure 1).[11] The degree of uncertainty regarding a decision will decrease when the result of an NIT is combined with prior knowledge. This generates a posterior, or post-test, probability. The posterior probability is consequently a combination of (1) existing knowledge about the prevalence/incidence of the event under investigation, (2) test accuracy, and (3) the test result. For diagnostic tests, the positive and negative predictive values are post-test probabilities; these can be computed from the prevalence of the target condition and the pre-test probabilities, sensitivity, and specificity.[11] Most clinicians unconsciously incorporate prior and posterior probabilities for diagnostic decisions.[12] Prior probability takes known risk factors into account before the diagnostic test is applied. Therefore, the pre-test risk would be evaluated by considering risk factors such as comorbid conditions or the level of alcohol consumption.[10,13] For example, if a patient with compensated cirrhosis reports excessive alcohol consumption and has type 2 diabetes, a liver stiffness measurement (LSM) by transient elastography (TE) of 11 kPa will make the clinician less worried about rapid progression to decompensation than if TE yielded an LSM of 30 kPa. However, the clinician will not stop monitoring such a patient because the prior probability of decompensation in 1–4 years remains high.[14]

The cutoff is another important concept in NITs that, on the one hand, makes them operational in decision-making, but on the other hand, compromises that information. The biology of chronic liver disease unfolds over a continuous spectrum. Similarly, most NITs provide results on a continuous scale, yet we use cutoffs to reduce them to a binary result: yes-no, normal-abnormal, and positive-negative. This simplification is necessary because many treatment decisions involve binary options; however, there may be an inherent loss of data.[15] Importantly, continuous scales may however still be used to increase or decrease a clinician's confidence in their decision. For example, the ANTICIPATE study developed an algorithm to transform TE and platelet count into a predicted probability of varices needing treatment for patients with compensated advanced chronic liver disease (cACLD), ranging from 2.5% to 60%.[16] Nevertheless, the predicted probabilities from ANTICIPATE were quickly reduced to the binary Baveno VI criteria for avoiding upper endoscopies[17]: A TE of 20 kPa and platelet count of 150×10^9/L corresponded to a 5% predicted risk of varices needing treatment, and values beyond those thresholds were deemed too risky for missing varices needing treatment.[16]

To minimize data loss when using NITs, most diagnostic NITs have rule-in and rule-out cutoffs for the same diagnostic target. A cutoff with a sensitivity above 90%–95% is likely to reduce false negatives to an acceptable level in a patient with lower values, while a cutoff with a specificity above 90%–95% in a patient with higher values can likely reduce false positives to an acceptable level.

Natural history of hepatic decompensation

Meaningful application of NITs depends on knowledge of prior probabilities and of disease stages, and the natural

TABLE 1 Examples of common clinical questions in hepatology, with decisions, health care settings, NITs used to support decisions, and invasive tests previously used

Question	Setting	Decision	NITs	Previously used invasive test
Is this patient at high risk of developing decompensation? Does she/he have cirrhosis?	Primary care	Refer to secondary care	Ultrasound, FIB-4, NFS, routine liver function tests, and liver enzymes	Liver biopsy
Does this patient have advanced fibrosis?	Secondary care	Send back to primary care	Advanced imaging, elastography, advanced liver blood tests	Liver biopsy
Is there a strong likelihood that this patient has varices that need treatment?	Outpatient liver clinic	Perform upper endoscopy	TE, platelet counts, (spleen stiffness)	Endoscopy in all
Will this patient benefit from treatment to reduce portal pressure?	Outpatient liver clinic	Initiate carvedilol or NSBBs	TE, platelet counts	HVPG measurement
Does this patient have covert HE?	Outpatient liver clinic	Initiate lactulose	Psychometric tests	N/A
Why does HE persist in this patient despite treatment with lactulose and rifaximin?	In- or outpatient care	Embolize collaterals	CT, MRI	N/A
Does this patient have sarcopenia?	In- or outpatient care	Refer to a dietician. Recommend resistance training	CT, MRI, DXA, BIA, handgrip test	N/A
Is this patient at high risk of developing SBP?	Inpatient or outpatient care	Initiate prophylactic antibiotics	Ascites protein	N/A
Will survival probabilities improve substantially for this patient if he/she receives a liver transplant?	Outpatient liver clinic	Refer to the liver transplant unit	MELD, echocardiography, CT, MRI, alcohol biomarkers	N/A
Will this patient's chances of survival increase with more intensive treatment?	Inpatient care	Transfer to specialized intensive care unit	CLIF-C scores, MELD, SOFA score	N/A

Abbreviations: BIA, bioelectrical impedance analysis; CLIF-C, European Foundation for the Study of Chronic Liver Failure Consortium; DXA, dual-energy x-ray absorptiometry; FIB-4, Fibrosis 4 Index; NFS, NAFLD fibrosis score; NIT, noninvasive test; NSBBs, nonselective beta-blockers; SOFA, Sequential Organ Failure Assessment; SBP, spontaneous bacterial peritonitis; TE, transient elastography.

history of cirrhosis should therefore always be considered.[18] Decompensation events are important milestones for patients with cirrhosis (Figure 2). However, the definitions of these events vary due to differences in study methodologies, historical changes, health care policies, and sociodemography.[18,19] Homogenous definitions of compensated cirrhosis and the events that define decompensation are important for comparing studies and ensuring the transfer of knowledge. Cirrhosis is a histological diagnosis defined as architectural changes and morphological deterioration of liver tissue and characterized by the presence of regenerative nodules.[20] Because architectural changes may be heterogeneously distributed in a cirrhotic liver, and liver biopsies are prone to sampling errors, imaging is important for the diagnosis of cirrhosis. Over the past 20–30 years, we have realized that the transition from fibrosis to cirrhosis is a continuum, and this understanding has changed the focus from the histological diagnosis to complications, which are more distinctive.[20] Development of portal hypertension due to fibrotic and vascular changes is a hallmark of the earliest complications of cirrhosis, with clinically significant portal hypertension (CSPH) being the key event for increased risk of ascites, variceal bleeding, and other decompensations.[17] For this reason, the current consensus is to use the more operational term "cACLD" in preference to the histological term "cirrhosis."[17,21] There is a seamless transition between severe fibrosis (F3) and cirrhosis. The term "cACLD" refers to a condition in which (a) the liver has chronic damage that affects its function, and (b) portal hypertension is emerging but in which compensatory physiological mechanisms are still able to maintain the patient in an asymptomatic or mildly symptomatic state. Consequently, cACLD is characterized by the presence of clinical, biochemical, and/or imaging findings that suggest liver dysfunction, although the patient experiences only mild symptoms at worst. Importantly, the current definition of cACLD is based on TE, not liver histology (Table 2). Depending on availability, other NIT results may be used to evaluate patients in clinical practice. For example, cirrhosis or portal hypertension stigmata detected by imaging; point shear-wave elastography (pSWE) <9 kPa rules out cACLD, whereas pSWE ≥13 kPa suggests cACLD in patients with metabolic dysfunction–associated steatotic liver

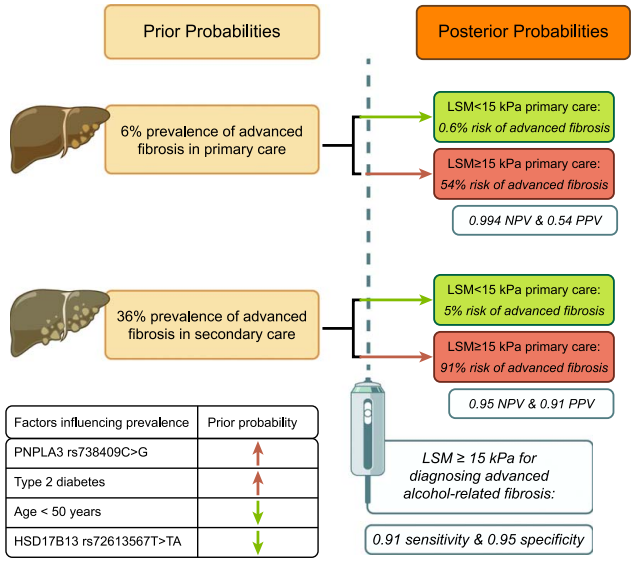

FIGURE 1 Bayes theorem exemplified by transient elastography for diagnosing advanced alcohol-related fibrosis in primary versus secondary care. Prevalences and the sensitivity and specificity of transient elastography are taken from Thiele et al.[9] The prior probability denotes the risk of advanced fibrosis before having the test result. In a diagnostic setting, the prior probability equals the prevalence; in a prognostic setting, it equals the incidence. Posterior probabilities denote the risk assessment after the test result is obtained. In a diagnostic setting, this is similar to the positive and negative predictive values. In the example, the risk for advanced fibrosis in a patient from primary care with liver stiffness below 15 kPa is calculated as:

$$1-\mathrm{NPV}=1-\left(\frac{specificity\times(1-prevalence)}{specificity\times(1-prevalence)+(1-sensitivity)\times prevalence}\right)$$
$$=1-\left(\frac{0.95\times0.94}{0.95\times0.94+0.09\times0.06}\right)=1-0.994=0.6\%$$

.

The posterior probability is consequently highly dependent on both test accuracy and disease prevalence. From this example, it is also clear that if transient elastography is performed in primary care, a result of 15.2 kPa should be interpreted differently from the same result for the same patient in secondary care. In primary care, slightly more than half of patients with LSM ≥ 15 kPa have advanced fibrosis, compared to 91% of patients in secondary care. Knowledge of predisposing factors that influence prevalence will also affect posterior probability. Examples from Israelsen et al.[10] Abbreviation: LSM, liver stiffness measurement (transient elastography).

disease (MASLD) and chronic viral hepatitis; and a spleen stiffness TE measurement <40 kPa rules out CSPH.[22,23]

First hepatic decompensation

Decompensation is the presence of complications of portal hypertension and/or liver dysfunction and it is frequently diagnosed at hospital admission.[18] Recently, 2 conceptually different types of decompensation were described: acute and nonacute.[24]

A first decompensation event is often nonacute and occurs when decompensation follows a slow and subclinical period of several months or years before the symptoms become severe enough to require medical treatment. The development of ascites is frequently the first nonacute decompensation event, observed in one-third to half of the patients; but hyponatremia and hypoalbuminemia commonly follow a similar nonacute trajectory.[25] Nonacute decompensation debuts with only 1 decompensating event in 50%–72% of cases.[24,25]

Acute decompensation involves rapid development of decompensation within a few weeks.[26] This occurs more frequently in patients with previous decompensation, but in patients who exhibited acute decompensation as the first presentation of liver disease, it is often predisposed by signs of portal hypertension or liver failure.[27] The intensity and severity of the first decompensation seem to be prognostic.[28] Likewise, patients who exhibit acute-on-chronic liver failure (ACLF) as their first decompensation have poorer outcomes than other patients with previous hospitalizations.[26,29] Similarly, the MELD score at the first decompensation event is closely associated with the outcome.[30]

Precipitating events precede decompensation. These events need to be of sufficiently high intensity to overwhelm the body's stabilizing mechanisms and cause impairment of organ function, triggering decompensation.[29] The PREDICT study in Europe identified severe alcohol-associated hepatitis and/or bacterial infection as precipitating events in >60% of cases.[29] However, in 30%–40% of cases, no precipitating events were identified.[31] In these cases, bacterial translocation may cause acute deterioration, a hypothesis supported by recent metabolomics data.[32,33]

Further hepatic decompensation

Further decompensation marks a prognostic deterioration in a patient who has already experienced his/her first hepatic decompensation. The further decompensating event is the occurrence of any of the following: (a) a second type of portal hypertension-driven decompensation (ascites, variceal bleeding, or HE, except if HE occurs in relation to bleeding); (b) jaundice; (c) recurrent variceal bleeding, recurrent ascites, or recurrent HE; (d) spontaneous bacterial peritonitis; or (e) hepatorenal syndrome (HRS)-acute kidney injury (AKI).[3]

Further decompensation can present as acute decompensation caused by a sequential or simultaneous combination of portal hypertension and systemic inflammation. The severities of these key pathophysiological factors predict the outcome of acute decompensation, perhaps with systemic inflammation as the dominant prognostic driver.[27,34,35] In line with this, recent data from hospitalized patients demonstrated that although complications related to CSPH alone (such as variceal

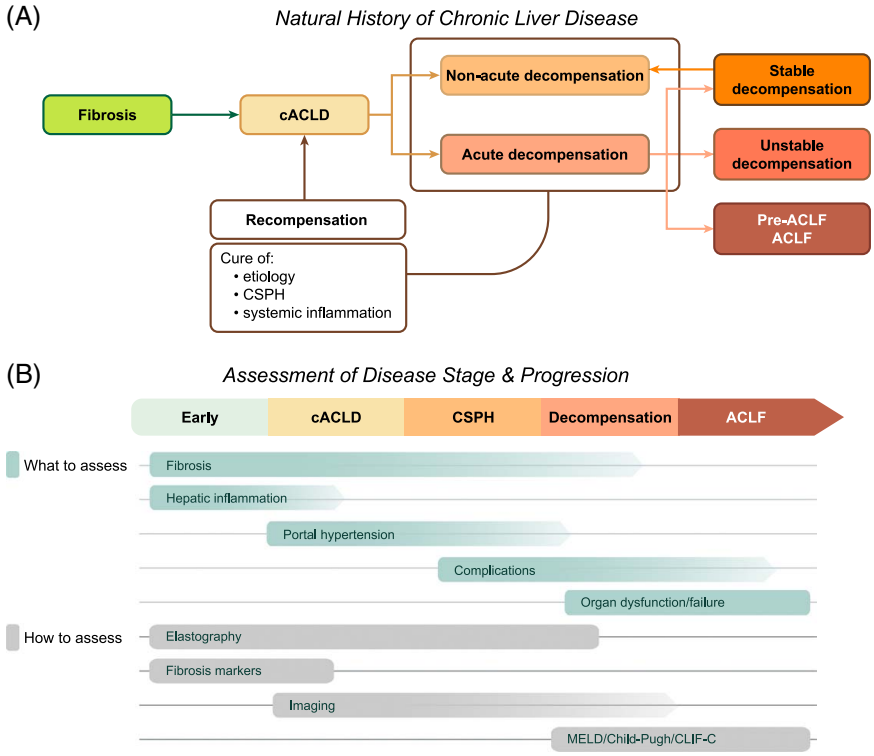

FIGURE 2 (A) Natural history of chronic liver disease. (B) NITs to be used according to the clinical spectrum of chronic liver disease. NITs for liver disease begin with diagnosing liver fibrosis and hepatic inflammation, progress to identification of portal hypertension, and culminate with monitoring complications and their treatment, organ failure, and death. Abbreviations: ACLF, acute-on-chronic liver failure; cACLD, compensated advanced chronic liver disease; CSPH, clinically significant portal hypertension; NIT, noninvasive test.

bleeding) are becoming less frequent, complications related to systemic inflammation (such as ascites, bacterial infections, and organ dysfunction) are becoming more frequent.[19]

ACLF and the so-called unstable decompensation are 2 highly vulnerable subgroups of further decompensation at higher risk of hospitalization, rehospitalization, and mortality. ACLF is a life-threatening deterioration from acute decompensation. In the PREDICT study, patients with ACLF at index hospitalization, or those who developed ACLF within 90 days, had particularly high levels of systemic inflammation markers and a poorer prognosis than patients with acute decompensation only.[27,36]

Hepatic recompensation

Cure or removal of etiological factors hugely benefits the further course of disease, even after decompensation; this has been demonstrated for patients with chronic viral hepatitis after antiviral treatment and for patients with alcohol-associated liver disease (ALD) who maintained abstinence.[37–41] Disease stabilization after the removal of etiological factors seems to be driven by amelioration of both portal hypertension[42] and systemic inflammation.[43] The concept of recompensation should however be interpreted with caution, as it requires regression of the structural and functional changes associated with cirrhosis, meaning substantial long-term improvements in liver synthesis function and results for NITs for fibrosis, as well as the discontinuation of medication to counteract complications [eg, diuretics, lactulose, and nonselective beta-blockers (NSBBs)].[3]

Furthermore, even after recompensation, the physiological memory of decompensation is apparently retained as an overactive inflammasome pathway dominated by IL-1β.[34,43] The inflammasomes of compensated patients who progress to ACLF differ from those of recompensated patients who develop ACLF.[43,44] This overactive systemic inflammation can predict decompensation, even when CSPH is abolished.[45] For example, patients with TIPS and high levels of systemic inflammatory markers in the hepatic vein are at high risk of further decompensation despite normalization of portal pressure.[46]

Types of NITs

A variety of NITs are used in the management of decompensated cirrhosis. These can be divided into circulating markers, elastography-based tools, imaging tools, and algorithms that combine several NITs. These tools are useful at different stages of chronic liver

TABLE 2 Transient elastography diagnostic rules for cACLD, CSPH, and varices needing treatment according to the Baveno VII consensus

Diagnosis of cACLD		
Rule out	Intermediate	Rule in
TE <10 kPa in the absence of other known clinical/imaging signs	TE 10–14.9 kPa	TE $\geq$ 15 kPa
Diagnosis of CSPH		
Rule out	Intermediate[a]	Rule in for viral, ALD, and nonobese NASH[b]
TE $<$ 15 kPa and platelet count $\geq 150 \times 10^9$/L[c]	TE $<$ 15 kPa and platelet count $< 150 \times 10^9$/L or TE 15–19.9 kPa and platelet count $\geq 110 \times 10^9$/L or TE 20–24.9 kPa and platelet count $\geq 150 \times 10^9$/L	TE 15–19.9 kPa and platelet count $< 110 \times 10^9$/L, or TE 20–24.9 kPa and platelet count $< 150 \times 10^9$/L, or TE $\geq$ 25 kPa.
Varices needing treatment		
Endoscopy not needed	Endoscopy needed	—
TE $<$ 20 kPa and platelet count $\geq 150 \times 10^9$/L or Already on nonselective beta-blockers/carvedilol	TE $\geq$ 20 kPa or platelet count $< 150 \times 10^9$/L or Decompensated cirrhosis	—

[a]For viral, ALD, and nonobese NASH, use the ANTICIPATE model to predict CSPH in intermediates.[1]
[b]For obese NASH, use the ANTICIPATE-NASH model to predict CSPH.[2]
[c]After sustained virologic response in patients with cACLD with HCV, TE $<$ 12 kPa and platelet count $> 150 \times 10^9$/L rules out CSPH in the absence of co-factors.[3]
Abbreviations: ALD, alcohol-associated liver disease; cACLD, compensated advanced chronic liver disease; CSPH, clinically significant portal hypertension; kPa, kilopascal; LSM, liver stiffness measurement; TE, transient elastography.

disease: for diagnosis of fibrosis, cACLD, CSPH, and decompensation events; for prognostication in compensated and decompensated patients; and for monitoring responses to therapy (Figure 2).

NITs are useful alternatives to avoid resource-heavy, invasive procedures such as liver biopsies, endoscopy, and hepatic vein catheterization; they are patient-friendly, less costly, more rapid, and easy to repeat.[47–49] Furthermore, NITs such as elastography and ultrasound allow for point-of-care assessments.

Circulating markers

Circulating, or blood-based, biomarkers are the most widely used in the management of chronic liver disease. Blood-based markers can be classified as patented and nonpatented. The labels “indirect” and “direct” markers are used exclusively for circulating markers of fibrosis.[6]

In 2016, the FDA defined a biomarker as “a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention.”[50] This broad definition encompasses all routine blood tests used to evaluate current states and predict the future of patients at risk of decompensation.[51] Three categories of markers are particularly important for liver disease: markers of the extracellular matrix, of inflammation, and of circulatory dysfunction.

The hepatic extracellular matrix is a dynamic structure that is constantly remodeled, even after decompensation.[52] Circulating levels of collagen types I, III, IV, V, and VI all increase with disease severity and correlate with portal hypertension.[53] Consequently, patented extracellular matrix markers such as the Enhanced Liver Fibrosis (ELF) test (Siemens Healthcare) and PRO-C3 (Nordic Bioscience) exhibit good diagnostic and prognostic accuracy for advanced fibrosis.[4,54–56] Importantly, an imbalance between excessive collagen type III formation versus reduced removal predicts both the progression of fibrosis and deterioration of already decompensated patients.[57,58]

Hepatic inflammation is another pathophysiological driver of liver disease progression.[59,60] Subclinical proinflammatory signaling and immune dysfunction have been linked to the pathophysiology of fibrosis, the risk of decompensation, ACLF, bacterial infections, and mortality.[61–63] Levels of cytokeratin-18 markers of hepatocyte damage correlate with steatohepatitis; levels of macrophage activation marker soluble CD163 correlate with hepatic inflammation, fibrosis, and portal hypertension; and levels of cytokines such as IL-6 correlate with decompensation and mortality rates.[64–67]

However, none of these markers have been adopted in clinical practice. At present, routine blood tests such as transaminases, gamma-glutamyl transferase, ferritin, and C-reactive protein, as well as white blood cell counts, are the only circulating markers that are used to guide decisions regarding inflammation and infections in patients with cirrhosis.

Finally, circulatory dysfunction strongly predicts first and further decompensation.[68] Low mean arterial blood pressure and a high heart rate are characteristics of a hyperdynamic circulation in patients with cirrhosis, whereas the hormones renin, angiotensin, aldosterone, vasopressin, and norepinephrine are not commonly used in a clinical setting, despite their well-established roles in the pathways driving circulatory dysfunction.[69–71]

Elastography and imaging tools

Elastography quantifies tissue elasticity. In hepatology, this technique takes advantage of the fact that liver fibrosis makes the liver stiffer, resulting in higher velocities of shear waves induced by vibration of the liver.[72] Liver stiffness is measured as shear-wave velocities induced either by a low-frequency vibrator for TE (FibroScan; Echosens, France) and magnetic resonance elastography (MRE), or by acoustic radiation force imaging from the ultrasound probe for pSWE and 2-dimensional (2D)-SWE (various manufacturers).[73] The greatest advantage of these techniques is that, with the exception of MRE, they can be used for point-of-care bedside assessment after the instrument operators receive some basic training. Furthermore, MRE, pSWE, and 2D-SWE provide conventional imaging of the liver in parallel with the elastography measurements. All of these techniques can also provide estimates of steatosis, with the MRI-proton density fat fraction technique having the highest accuracy and sensitivity.[74]

Ultrasound, CT, and MRI all assess imaging evidence of cirrhosis and portal hypertension.[75] Although ultrasound is associated with greater operator-based variability and reduced image quality in patients with obesity, it is cheap, can be applied at the point-of-care, and is the standard method used for HCC surveillance.[76]

CT can not only detect esophageal varices, but it can also be used to measure the total area of spontaneous portosystemic shunts as a predictor of HE and mortality.[77,78] However, none of the imaging modalities can rule out cACLD due to low sensitivity for liver fibrosis in compensated patients.[79]

Models and algorithms

Models and algorithms combine tests, either simultaneously and in parallel or sequentially, with an index test first to determine whether a second test is necessary. By combining different types of information, algorithms can provide superior information to guide decision-making, compared with individual tests alone. We describe the following widely used algorithms in subsequent sections: the fibrosis 4 index (FIB-4), the Baveno VI criteria, the MELD, the Child-Pugh score, and the European Foundation for the Study of Chronic Liver Failure Consortium score.[6,80–82]

Diagnostic tools for noninvasive assessment of hepatic decompensation

There is considerable overlap between diagnosing, staging, and risk prediction in chronic liver disease. In some cases, the development of NITs has defined diagnoses such as cACLD. In this section, we discuss how to establish these diagnoses in clinical practice, recognizing the probabilistic nature and inherent uncertainty of any diagnostic process.

Diagnosis of liver fibrosis and compensated advanced chronic liver disease

Over the last 2 decades, elastography has transformed the early identification of patients at risk of hepatic decompensation due to its accuracy in diagnosing severe fibrosis and cirrhosis.[83] The severity of liver fibrosis is the strongest predictor for the development of hepatic decompensation and liver-related mortality in patients with asymptomatic chronic liver disease.[5,84] Although elastography cannot reliably distinguish between individual fibrosis stages, the Baveno VII rule of 5 for TE provides an opportunity for noninvasive staging of patient risk as follows.[3] A TE value of 5 kPa (LSM) is normal, and no further investigations are needed. A TE value of <10 kPa denotes a very low risk of decompensation and can consequently be used to refer patients with MASLD or ALD back to primary care.[4,85] TE values above 15, 20, or 25 kPa, in combination with platelet counts denote high risks of CSPH and decompensation (Table 2). It has been suggested that these cutoffs could also be used as decision thresholds to initiate treatment with NSBBs in patients with cACLD to prevent decompensation.[3,86] An unresolved issue is whether different thresholds should be applied for different etiologies.[87] Since the risk of liver-related events for a given category of “the rule of five” is substantially different for ALD than for other etiologies, an increase in LSM results in higher relative risks of decompensation, whereas absolute risks may differ substantially across other etiologies. However, uniform TE thresholds for all etiologies considerably simplify the cACLD concept, and prognostic differences between etiologies could be

captured by more frequent assessments of patients with more active liver disease (eg, nonabstinent patients with ALD).

A major unresolved issue regarding MRE, pSWE, and 2D-SWE concerns the various devices that provide values of liver stiffness that are not identical. The Society of Radiologists in Ultrasound recently suggested the following vendor-neutral "rule of four" for pSWE in chronic viral hepatitis and MASLD. A pSWE value of 5 kPa (1.3 m/s) is normal; a pSWE value of <9 kPa (1.7 m/s) rules out cACLD, except in some patients with MASLD where the cutoff may be as low as 7 kPa (1.5 m/s); and a pSWE value of ≥13 kPa (2.1 m/s) strongly suggests cACLD.[23]

The levels of indirect markers [eg, AST, ALT, and platelets] are not directly correlated with fibrosis and are inaccurate alone for the assessment of liver fibrosis.[88] Accuracy can be increased when combined in models such as the FIB-4 and nonalcoholic fatty liver disease fibrosis score (NFS), but these indirect models are poor at ruling in advanced fibrosis.[6,89] Instead, they are more effective as the first step in a 2-step strategy in which, for example, all patients with a FIB-4 value ≥ 1.30 are referred for elastography or testing based on commercial or circulating markers.[90]

Diagnosis of clinically significant portal hypertension

The PREDESCI randomized controlled trial and a subsequent meta-analysis have shown the efficacy of beta-blockers in preventing hepatic decompensation in patients with CSPH.[91,92] However, in the PREDESCI trial, CSPH was diagnosed by measuring the HVPG, not by NITs.

Noninvasive diagnosis of CSPH is currently based on TE. ANTICIPATE is a regression model that estimates the probability of CSPH based on LSMs (TE) and platelet counts (Table 2).[16] It has been externally validated for cACLD related to untreated hepatitis C, ALD, and nonobese MASLD.[93] In patients with cACLD related to MASLD and obesity, a recent study suggested that the ANTICIPATE model overpredicted CSPH, leading to the development of a corrected model (the ANTICIPATE-NASH model) that took body mass index (BMI) into account.[93] This was because BMI altered the correlation between LSMs (TE) and HVPG (ie, for a given LSM, the higher the BMI, the lower the HVPG). In a subsequent study of patients with more advanced liver disease, both models (ANTICIPATE and ANTICIPATE-NASH) performed well in predicting CSPH.[94] This suggests that the effect of BMI loses relevance, compared with the effects of liver stiffness and platelet counts, in patients with more advanced disease.

Another relevant question is whether the same thresholds to diagnose CSPH are applicable for patients in whom disease activity has been controlled. This has been addressed mainly in the context of hepatitis C,[95] because a sustained viral response alters the relationship between HVPG and combined LSMs plus platelet counts. After a sustained virologic response, for a given value of LSM combined with platelet count, the HVPG value was lower than that observed before treatment, resulting in different thresholds for excluding the presence of CSPH.

Finally, spleen stiffness measurements (SSMs), measured by TE, have been proposed to enhance the diagnosis of CSPH, although this technique was mainly investigated in patients with hepatitis C, in whom enlarged spleens allow for acceptable failure rates.[96,97] Consequently, further studies are needed to investigate the performance of SSM in other etiologies, with spleen-specific probes, and with techniques other than TE.[98,99] In patients with cACLD, SSM by TE values of <40 kPa may rule out CSPH, whereas SSM values of ≥40 kPa (when LSMs are in the range 15–25 kPa) may rule in CSPH.[96] A screening strategy that combines LSMs and SSMs has been validated for detecting varices needing treatment in a randomized trial of patients with viral hepatitis.[22] During 3.5 years of follow-up, there was no difference in the rate of variceal bleeding (4.4% vs. 4.0%, $p = 0.724$) or hepatic decompensation in patients referred for endoscopy based on LSM ≥12.5 kPa or SSM ≥41.3 kPa, versus those who were all referred for endoscopy.

Diagnosis of decompensation: varices, ascites, and HE

The recent definition of first cirrhosis decompensation includes variceal bleeding, moderate and large amounts of ascites, and overt HE.[3] However, less severe evidence of portal hypertension exists, and an ordinal score that includes the presence of varices without bleeding, minimal ascites, and covert HE could be useful to improve the efficiency of future randomized trials involving compensated cirrhosis.

Until 2015, the paradigm for variceal screening in cirrhosis was for all patients to undergo gastroscopy. With the development of NITs, this paradigm changed to a 2-step strategy in which patients with cACLD would only undergo gastroscopy if LSMs (TE) were ≥20 kPa or platelet counts were <150 (Baveno VI criteria).[17] These criteria were extensively validated for all etiologies (the pooled negative predictive value for high-risk varices was 99%),[100] including after the suppression of the primary etiological factor,[3,101] and have been widely implemented in clinical practice. Subsequent attempts to expand these criteria resulted in lower negative predictive values, and the expanded criteria

are not currently recommended.[3] Similarly, there are no validated algorithms that use alternatives to LSMs obtained by TE. Although the Baveno VI criteria may become less relevant if treatment with NSBBs for CSPH becomes the norm, a substantial proportion of patients will have contraindications or intolerance to NSBBs and will therefore need to be assessed for endoscopy.[86]

The presence of ascites is commonly clinically overt. However, patients with compensated cirrhosis have regular ultrasound examinations, which occasionally detect small amounts (grade 1) of ascites. Although minimal ascites are not considered decompensation, affected patients appear to have poorer prognoses.[102,103] Interestingly, grade 1 ascites were not associated with a higher rate of progression to overt ascites,[102] suggesting that these patients do not necessarily need diuretic treatment, but it was associated with a higher level of systemic inflammation as compared with no ascites.[102]

Overt HE (West Haven grade ≥ II) is usually diagnosed on clinical grounds, but because normal values of plasma ammonia rule out overt HE with a high negative predictive value, measurement of ammonia may be done in patients with acute encephalopathy to exclude other causes of cognitive impairment.[104] On a more exploratory note, elevated levels of ammonia have shown to predict hospitalization with liver-related complications in stable outpatients with cirrhosis.[105] However, one should be aware that measuring and using serum ammonia has limitations including handling and processing time of the sample having a significant impact on the ammonia levels. Further, no upper limit of normal or generally accepted diagnostic cutoff exists, and ammonia levels overlap in patients with HE of various grades.[106–108]

A diagnosis of covert HE requires neuropsychological or psychometric tests.[104] These tests include the simple Animal Naming Test, for bedside use, and the gold standard psychometric HE score.[104,109] Because covert HE is associated with a higher risk of overt HE and impaired patient-reported outcomes, EASL guidelines suggest screening for covert HE and treatment with lactulose if present, even if supported by a low level of evidence.[110]

Prognostic tools and predictive factors of decompensation

Prognostic biomarkers quantify the likelihood of clinical events, disease recurrence, or disease progression.[50] As transitioning from a compensated to decompensated state is the single most important factor affecting survival in patients with cirrhosis, the prediction of decompensation is a major prognostic target.[111] The etiology of the liver disease is essential for prognostication. In a recent prospective study on the natural history of MASLD, 11% of patients with compensated cirrhosis at baseline decompensated during 4 years of follow-up.[5] By comparison, patients with ALD cirrhosis exhibit a 4-fold higher risk of decompensation (Figure 3).[4] Such substantial differences in the risks of decompensation in different etiologies call for individualized use of prognostic tests, especially in terms of monitoring intervals and post-test probabilities.

Prognostics in primary care

Prognostic NITs in primary care must be widely accessible and inexpensive. Patient selection may be used to increase the pre-test risk of disease and reduce

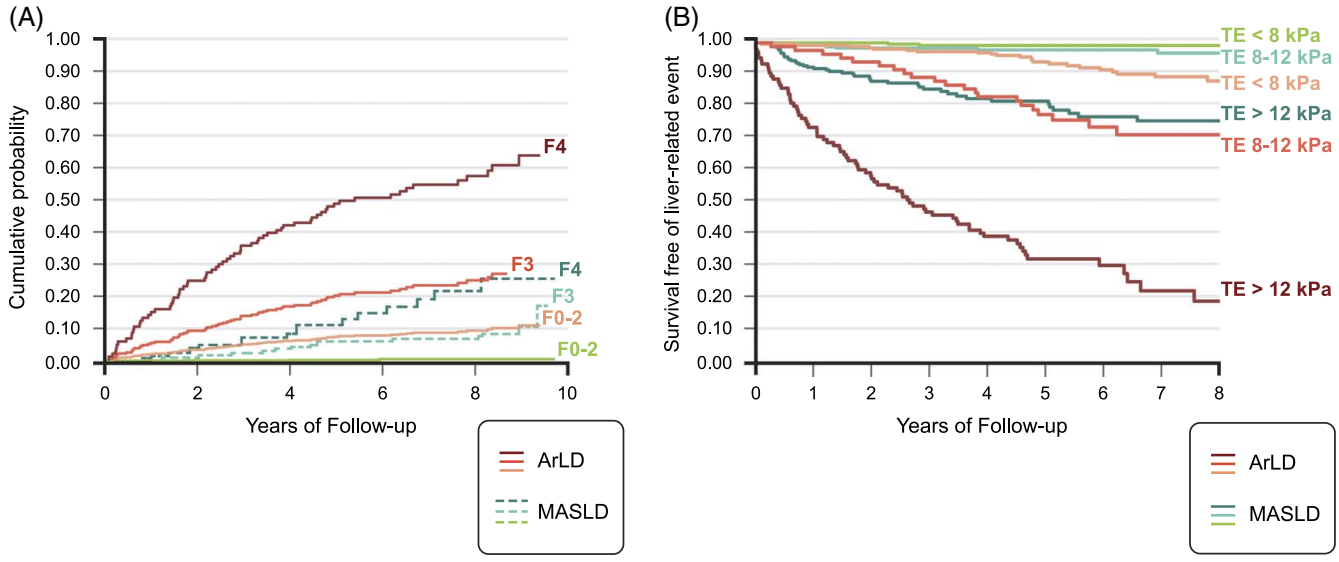

FIGURE 3 (A) Risk of hepatic decompensation stratified by baseline fibrosis stage and etiology. (B) Risk of hepatic decompensation stratified by baseline transient elastography value and etiology. Adapted from Rasmussen et al.[4] and Boursier et al[112]

the costs associated with NITs.[113–115] However, a recent study showed that pre-test risk stratification based on predictors such as long-term excessive alcohol intake, binge drinking, diabetes, insulin resistance, dyslipidemia, waist circumference, and obesity missed up to 50% of those who subsequently developed liver events.[116]

The FIB-4 combines AST and ALT levels, platelet counts, and age into a simple algorithm. FIB-4 is the current standard for prognostication in primary care due to its wide availability and amenability to automation within a biochemical testing system. A Swedish study of repeated FIB-4 measurements in 40,729 patients from the general population showed that transitioning from a low (< 1.30) or intermediate (1.30–2.66) to a high FIB-4 value (≥2.67) was associated with a higher risk of developing severe liver disease (adjusted HR of ~8). Nevertheless, FIB-4 is limited by its poor sensitivity because half of all cases of severe liver disease happened in patients with a low or intermediate FIB-4 value.[117] Alternatives to FIB-4 exist but are not as extensively validated; these include the NFS, AST-platelet ratio index, and the Forns index.[118]

Sarcopenia and frailty are prevalent in patients with cirrhosis, and recognizing these conditions is critical due to the associations with poor outcomes and poor quality of life. The primary care physician can contribute to the assessment by using tests like a 6-minute walk test, the assessment of handgrip strength, the mid-arm muscle circumference, or a screening for dietary protein intake.[119]

Genetic information has the potential to transform risk stratification because our genes are preserved characteristics of risk or resilience that are with us from conception. As genetic testing is currently not available in primary care, risk stratification using genetic information is a promising future direction. The patatin-like phospholipase domain-containing protein 3 p.I148M missense variant is present in >20% of the global population and increases the risk of steatosis, cirrhosis, and HCC across etiologies.[120] Other single nucleotide variants with high effect sizes for cirrhosis risk include missense polymorphisms at SERPINA1 and TM6SF2 and a loss-of-function polymorphism at HSD17B13.[121] Genetic risk scores combine several risk polymorphisms and may potentially identify patients at risk of cirrhosis from birth, although they lack adequate discriminative power when the onset of disease is only 5–10 years away.[122,123] Polygenic risk scores combine hundreds or thousands of genetic risk alleles in an attempt to quantify an individual's total genetic risk of cirrhosis.[124] A recent study combined 12 genetic risk alleles. The 20% of patients with the highest polygenic risk had more than twice the odds of cirrhosis, compared to the 20% of patients at the lowest risk of cirrhosis.[123] The total fraction of elevated genetic risk for cirrhosis attributable to the population was 55%, highlighting that modifiable environmental factors must be included for prognostic genetic risk scores to have sufficient discriminative accuracy.[125]

Elastography to predict decompensation

An LSM by TE is the best validated prognostic marker for determining liver-related morbidity and mortality in patients with compensated liver disease. A study of 3028 patients with mixed etiologies found a cumulative incidence of decompensation of 3.7% after 5 years for patients with TE values <15 kPa, increasing to 19% for patients with baseline TE values ≥25 kPa.[126] In 462 patients with early ALD, TE outperformed the biopsy-verified fibrosis stage as a prognostic marker, with a C-index for liver-related events of 0.876.[4] During 4.1 years of follow-up, liver-related events occurred in 3% of patients with TE values <10 kPa, 21% of patients with TE values of 10–15 kPa, and 54% of patients with TE values ≥ 15 kPa. TE performs equally well in patients with MASLD, with a *C*-index for prediction of liver-related events of 0.878.[112] However, for comparable TE cutoffs MASLD is associated with lower risks than ALD. Of 594 patients with MASLD followed for 3.1 years, 0.5% of those with TE values <8 kPa, 3% of those with TE values of 8–12 kPa, and 16% of those with TE values > 12 kPa experienced liver-related events (Figure 3B).[112]

The prognostic range of TE is from 5 to 25 kPa. A dose–response meta-analysis observed a steep increase in the relative risk of decompensation with increasing TE values up to 25 kPa, from which the relative risk did not increase further.[127]

Other elastography techniques such as pSWE, 2D-SWE, and MRE also exhibit comparable accuracy as prognostic markers of decompensation and mortality, but variation in published cutoffs and heterogeneity attributable to equipment from different manufacturers limit their generalizability.[128,129]

Blood-based prediction of hepatic decompensation

Blood-based fibrosis markers also exhibit prognostic accuracy in secondary care. In a systematic review of 10,162 patients with MASLD from 13 studies, the AUCs for liver-related events evaluated using the FIB-4 ranged from 0.72 to 0.89; the corresponding AUCs for events evaluated using the NFS ranged from 0.72 to 0.92, and for events evaluated using the AST-platelet ratio index they ranged from 0.60 to 0.89.[130] A large study of patients with MASLD from tertiary care found that FIB-4 and NFS were more accurate in predicting liver-related events during 3.4 years of follow-up than AST-platelet ratio index or BMI, AST/ALT ratio, and diabetes, with *C*-indexes just below 0.8.[131] In patients with ALD, FIB-4

had a slightly higher *C*-index of 0.821, whereas NFS and Forns index had indices just below 0.8.[4] Therefore, overall the results indicate a fairly good performance of these widely available scores in predicting decompensation within 3–5 years.

Like the nonpatented tests, patented markers such as the ELF, FibroTest, PRO-C3, FibroMeter, and others predict decompensation due to their correlation with advanced fibrosis. In general, they exhibit slightly higher prognostic accuracies than nonpatented tests. For example, ELF has an AUC of 0.87 for a 6-year prediction of decompensation and liver-related deaths in a mixed population, and a *C*-statistic of 0.86 for a 4.5-year prediction of liver-related events in patients with ALD.[4,132] However, all of the fibrosis markers perform best when they are tested in populations representing the full spectrum of fibrosis. In contrast, when a diagnosis of cirrhosis has been made, prognostic accuracy diminishes: The *C*-statistic of ELF was 0.68 for predicting liver-related events during a median of 2.6 years in 258 patients with metabolic dysfunction–associated steatohepatitis with compensated cirrhosis.[133]

Prediction of further decompensation and mortality

After the first decompensation, a second decompensating event drastically increases the likelihood of mortality within 5 years.[3,28] Further decompensations are driven less by fibrosis and more by hyperdynamic circulation, inflammation, immune dysfunction, and intrahepatic vascular resistance. Therefore, NITs of fibrosis are less clinically useful for predicting further decompensation.[127] Instead, algorithms and biomarkers of hepatic function predict the overall risk of further decompensation and short-term mortality, whereas specific biomarkers predict ascites, encephalopathy, and variceal bleeding, as described previously.

The MELD score was developed in 2000 for patients with TIPS, and validated in 2001 for predicting 3-month mortality in ambulatory and hospitalized patients with cirrhosis (*C*-statistic = 0.87).[80,134] This work was done to improve organ allocation, which until then was based on the Child-Pugh score and time spent on a waiting list. The MELD score combines creatinine and bilirubin measurements with INR. The score ranges from 6 to $\geq$ 40, with a MELD score $<$ 10 corresponding to a 1.9% risk of 3-month mortality, increasing to 6% for a MELD score of 10–19, 20% for a MELD score of 20–29, 53% for a MELD score of 30–39, and 71% for a MELD score $\geq$40. Because hyponatremia is a strong predictor of waiting-list mortality, the MELD score was revised to include serum sodium in 2008, and the MELD-Na is now in use for organ allocation in North America.[135] Recently, MELD 3.0 was developed, adding female sex, albumin, and interactions between laboratory parameters to the equation.[136] The latest MELD version improved discrimination for 3-month mortality (*C*-statistic = 0.87) and could potentially improve access to transplantation for female patients. The ~60-year-old Child-Pugh score has remained unaltered since R.N.H. Pugh and Roger Williams replaced nutritional status with prothrombin time in 1973; the original version was described by George Wantz and Mary Ann Payne in 1961, and by Child and Turcotte in 1964.[81,137,138] The score ranges from 5 to 15 and includes bilirubin, albumin, ascites, encephalopathy, and INR. The Child-Pugh score remains a robust algorithm for predicting mortality in patients with cirrhosis, but it has a smaller range than the MELD score, and the ascites and encephalopathy scoring components may be affected by operator variance. Both the MELD and Child-Pugh scores predict mortality more accurately in decompensated than compensated patients.[139] Other scores have been developed for particular populations, including the Albumin-Bilirubin grade for HCC patients with cirrhosis[140] and European Foundation for the Study of Chronic Liver Failure Consortium for hospitalized patients with ACLF.[82]

Monitoring response to therapy in patients with decompensated cirrhosis

Treatment of decompensation events is essential to cirrhosis management. Equally important is monitoring responses to treatment, which enables clinicians to adjust treatment duration and strategy, as well as evaluate treatment success. Furthermore, there is an unmet need to develop and validate predictive biomarkers that can identify patients who are most likely to benefit from treatments and those who are most likely to experience adverse events.

Monitoring response to diuretics in the treatment of ascites and edema

Ascites and edema develop with cirrhosis because of a marked alteration in the regulation of extracellular fluid volume. Sodium and associated water retention cause accumulation of extracellular fluid, which results in ascites and leg edema, leading to discomfort, impaired walking, and decreased quality of life.[141,142] Pharmacotherapy with aldosterone antagonists, alone or combined with loop diuretics, can increase sodium excretion.[141,143,144] The goal of this treatment is to achieve a negative sodium balance, which results in a negative fluid balance because water is eliminated with sodium. A low-sodium diet should also be implemented.

The ideal test for monitoring the efficacy of the treatment of ascites and edema would be an NIT to quantify fluid in extracellular spaces. Diuretics would be administered until fluid volume in the extracellular spaces had returned to normal. Unfortunately, such a tool does not exist. Instead, patients are monitored with less sophisticated tools that estimate the effect of treatment on total fluid (eg, by monitoring body weight). Alternatively, the biological effect of diuretics can be monitored easily by measuring changes in urinary sodium excretion (in mEq/day, measured accurately by 24 h urine collection).[141,143,144] An effective treatment of ascites is associated with a reduction in body weight of no more than 0.5–1 kg per day (1 kg if peripheral edema is also present). Effective diuretic treatment should increase sodium excretion compared to baseline, with 24 h sodium excretion exceeding the presumed sodium intake (90–100 mEq/day with a low-sodium diet). The major risks associated with such treatment include diuretic-induced AKI and hypovolemia (Table 3).

Monitoring response to beta-blockers after variceal bleeding

In patients treated with beta-blockers after variceal bleeding, it was shown that patients achieving an HVPG decrease below 12 mm Hg or by >20% from baseline had less complications of portal hypertension and improved survival.[145] This suggested that treatment should be tailored according to hemodynamic response, but the supporting evidence was limited to 1 randomized controlled trial,[146] which used drugs that are not currently recommended (nitrates and prazosin). The main limitation of monitoring therapy is the invasiveness, physiological variability and the cost of HVPG,[147] which limits the repeatability of measurements.[148] However, the use of NITs may make repeated assessments feasible for monitoring responses. Measuring spleen stiffness has generated promising initial results,[149,150] but further studies are needed specifically with repeated measurements over several days to confirm the consistency of the values.

Monitoring response to treatment of acute kidney injury

AKI occurs in up to 50% of patients hospitalized for complications of cirrhosis and is diagnosed on the basis of changes in serum creatinine.[143,144,151] As the success of AKI therapy is markedly dependent on early diagnosis, serum creatinine should be assessed in all patients with cirrhosis at hospital admission and frequently thereafter (ie, daily in patients in an intensive care unit and every 2–3 d in all other patients). According to the AKI management algorithm in recent international guidelines,[143,144] daily serum creatinine measurements should be used to monitor the effects of treatment to reverse AKI. Following this algorithm, more than one-third of AKI cases are resolved by day 3 and do not require further treatment. Therefore, monitoring of serum creatinine at day 3 of diagnosis of AKI is important.

An issue that has become relevant for clinicians caring for patients with cirrhosis and AKI is that of monitoring the treatment response of patients with HRS treated with terlipressin and albumin (Table 4). Response to terlipressin is defined either as a decrease in serum creatinine to values lower than 1.5 mg/dL at the end of therapy or, using a stricter definition, to values within 0.2 mg/dL of baseline (AKI resolution). Treatment with terlipressin is initiated at a dose of 2 mg/day using continuous i.v. infusion, and the effect on kidney function is monitored by measuring serum creatinine at 1- or 2-day intervals. If serum creatinine decreases by more than 25% of the pretreatment value after the first 48 hours of treatment, terlipressin is continued at the same dose. By contrast, if serum creatinine increases or remains stable,

TABLE 3 Clinical interpretation and therapeutic consequences of monitoring changes in body weight and urinary sodium excretion during diuretic therapy in patients with cirrhosis and ascites and/or edema

Body weight loss[a]	Increased 24 h sodium excretion[b]	Clinical interpretation	Therapeutic consequences
+	+	Positive response to diuretics	Maintain diuretic dose until ascites/edema decrease markedly. Then, reduce the dose by half
−	−	No response to diuretics	Increase diuretic dose and measure body weight and urine sodium after 1 wk
−	+	No compliance with a low-sodium diet	Provide patients and caregivers with appropriate information on a low-sodium diet
+	−	No response to diuretics associated with rapidly progressive malnutrition[c]	Increase diuretic dose Intensify nutritional support Consider alternative treatments for ascites

[a]Weight loss + indicates >1 kg within the first 7 days of therapy or >2 kg within 7 days thereafter.
[b]Increased 24-hour sodium excretion indicates urinary sodium greater than presumed sodium intake (usually >100 mEq/day).
[c]Occurs only infrequently.

TABLE 4 Proposed tools for monitoring treatment response to and adverse effects of terlipressin and albumin treatment in patients with cirrhosis and AKI-HRS

Tool	Interval	Therapeutic consequences/comments
Serum creatinine	2 d	Terlipressin dose adjustment according to changes[a]
Arterial pressure	6–8 h	Increase in mean arterial pressure >5% predicts response
Urine volume	daily	Diuresis increases in responder patients. Avoid bladder catheter if possible
Physical examination	8 h	Check for signs of ischemia in fingers, toes, skin, scrotum, etc.
Central blood volume status[b]	daily	If signs of central volume overload develop, stop albumin administration, stop/reduce terlipressin, and give furosemide i.v.

[a]After initiation of therapy, if serum creatinine decreases ≥ 25% of the pretreatment value after 2 days, terlipressin is continued at the same dose. However, if serum creatinine increases or remains stable, the dose of terlipressin is increased in stepwise intervals by 2 mg/day every 2 days until serum creatinine progressively decreases (maximum dose 12 mg/day).
[b]There is no consensus on which tools should be used to monitor central blood volume status.

the dose of terlipressin is increased stepwise in 2 mg/day intervals every 2 days up to a maximum 12 mg/day. Other markers of kidney function, such as BUN and cystatin-C, do not provide enough relevant information to be used in monitoring the response to terlipressin and albumin.

Monitoring arterial pressure as a surrogate marker of changes in systemic hemodynamics during therapy is also important.[152,153] An increase of >5 mm Hg in mean arterial pressure during therapy is an early predictor of treatment response. Urine volume may also be monitored because response to therapy is associated with increased diuresis. Nevertheless, bladder catheters should be avoided to prevent infections, except in patients with unstable conditions or associated severe HE. Because of the risk of pulmonary edema during treatment, central blood volume should also be monitored, but there is no consensus regarding the best monitoring method to use.[154] Finally, frequent clinical monitoring is advised to check for possible signs of peripheral ischemia in the fingers, toes, scrotum, skin, and tongue that may develop during therapy.[143,144,151]

In recent years, there has been interest in the potential role of kidney biomarkers for diagnosis and prognosis assessment of patients with cirrhosis and AKI.[155,156] The most promising results have been reported for studies on neutrophil gelatinase–associated lipocalin (NGAL). Several studies have demonstrated consistently that urine NGAL can be used to discriminate between AKI due to acute tubular necrosis and AKI due to HRS, the 2 more severe causes of AKI that are very difficult to diagnose on clinical grounds.[156–158] In particular, urine NGAL measured at day 3 after an AKI diagnosis is significantly higher in patients with AKI due to acute tubular necrosis than in those with AKI due to HRS. Values of urinary NGAL below the cutoff of 220–244 μg/g creatinine have a predictive accuracy of ≥ 0.8 for a diagnosis of HRS; therefore, they should be incorporated in the monitoring of patients with AKI in clinical practice. Moreover, low urine-NGAL values at day 3 after an AKI diagnosis also predict AKI resolution and improved short-term survival.

Monitoring response to antibiotics for spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis in cirrhosis occurs due to serious impairment of the immune system and may trigger severe complications, particularly AKI, HE, or ACLF; it is also associated with a high risk of mortality.[143,144] The diagnosis of spontaneous bacterial peritonitis requires a high index of suspicion because the clinical symptoms are heterogeneous and may not always include abdominal manifestations.[159] The biomarker used for diagnoses and for monitoring the efficacy of antibiotic therapy is neutrophil count in the ascitic fluid, and a bacterial isolate is not required for diagnoses because ascitic fluid culture is positive in less than half of cases. Other biomarkers based on systemic inflammation secondary to the infection, such as cytokines (eg, IL-6), pro-calcitonin, and others, have been investigated, but none have yet successfully shown to improve diagnostic accuracy. A summary of the changes in neutrophil count in ascitic fluid during antibiotic therapy and their clinical interpretations is presented in Table 5.

Monitoring response to treatment of HE

Development of overt HE requires rapid clinical investigation and initiation of therapy, including the management of possible precipitating factors.[109] Specific therapy of HE focuses on preventing ammonia absorption from the gut and reducing ammonia production. The response to treatment is generally monitored by evaluating neurological status every 6–12 hours on the same scales that are used to categorize disease severity, usually the West Haven criteria.[104,109] Psychometric testing is reserved for monitoring treatment effects on covert HE. There are no specific biomarkers for monitoring the response to therapy of patients with overt HE, but plasma ammonia levels may be informative because these decrease in patients improving from HE symptoms.[109] However, international guidelines do still

TABLE 5 Clinical interpretation and therapeutic consequences of changes in neutrophil counts in the ascitic fluid during antibiotic treatment of spontaneous bacterial peritonitis[16, 93, 95]

Baseline at diagnosis of SBP	Day 3	Clinical interpretation	Therapeutic consequences
250 cells/mm^3	Decrease ≥ 25% of baseline	Response to antibiotic therapy	Maintain the same antibiotic therapy in most circumstances or Deescalate antibiotic therapy if antibiotics against multidrug-resistant bacteria were given and multi-sensitive bacteria are isolated from an ascitic fluid culture
250 cells/mm^3	Decrease < 25% of baseline	No response to antibiotic therapy	Check ascitic fluid culture results: If positive, modify antibiotic therapy accordingly If negative, broaden antibiotic coverage, including multidrug-resistant bacteria if necessary, according to local bacteriological data Consider secondary bacterial peritonitis

not recommend the measurement of ammonia levels for monitoring the treatment of HE.

CONCLUSION

Compared with invasive tests, NITs are rapid, patient-friendly, cheap, and can often be used at the point-of-care. Accumulating evidence has documented their effectiveness in safely guiding clinical decision-making. Thus, NITs have become essential tools in the daily management and improved care of patients with cirrhosis. However, although there are data demonstrating the effectiveness of NITs for diagnosis and prognosis for most indications, there are limited data to support NITs as monitoring tools, and we need more data to understand the clinical meaning of changes over time. The goal is precision medicine with individualized approaches for each patient.[86] Omics and artificial intelligence technologies hold promise and may likely outperform current standards.[61] However, extensive validation, regulatory approval, and implementation of such tools for patients with cirrhosis may only be achievable in the longer term.

AUTHOR CONTRIBUTIONS

Aleksander Krag: Conceptualization. All authors: Writing—Original Draft. Maja Thiele and Stine Johansen: Writing—Review and editing and visualization. Aleksander Krag, Jonel Trebicka, and Pere Gines: Funding acquisition.

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CONFLICTS OF INTEREST

Maja Thiele advises GE Healthcare. She is on the speakers' bureau for Echosens, Norgine, Siemens Healthcare, and Tillotts Pharma. Jonel Trebicka consults and is on the speakers' bureau for CSL Behring, Gore, and Grifols. He is on the speakers' bureau for Boehringer-Ingelheim, Falk, GENFIT, and Versantis. Juan G. Abraldes received grants from Cook. Pere Gines consults and received grants from Ferring, Gilead, and Grifols. He consults for CSL Behring, Intercept, Martin Pharmaceuticals, Promethera, RallyBio, and Sequana. He received grants from Mallinckrodt. The remaining authors have no conflicts to report.

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